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(71) Applicant *(for GB IE only):* PFIZER LIMITED [GB/GB]; Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(71) Applicant *(for all designated States except GB IE US):* PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only) :* BANKS, Bernard, Joseph [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(74) Agents: MOORE, James, William et al.; Pfizer Limited, Patents Department, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

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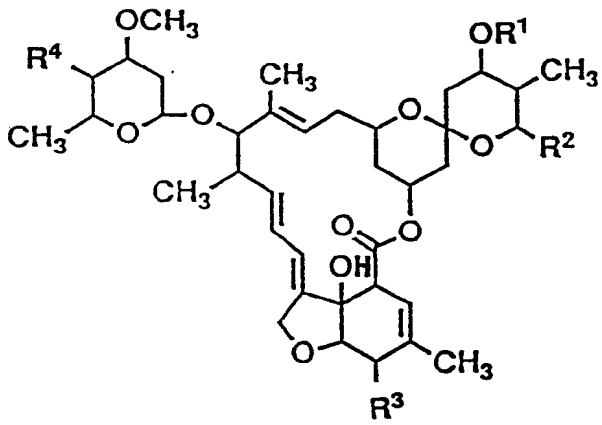
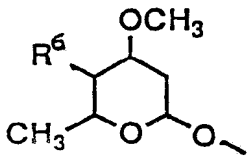


(I)



(II)

(57) Abstract

Compounds of formula (I) wherein R^1 is C_1-C_6 alkyl, C_3-C_6 alkenyl, or substituted C_1-C_4 alkyl wherein said substituent is halo, C_1-C_4 alkoxy, C_2-C_5 alkanoyl, C_2-C_5 alkoxycarbonyl, carboxy, mercapto or aryl; R^2 is C_3-C_8 alkyl, C_3-C_8 alkenyl, C_3-C_8 cycloalkyl or C_5-C_8 cycloalkenyl; R^3 is OH, C_1-C_4 alkoxy or C_2-C_5 alkanoyloxy; or R^3 is linked by a double bond and is $=N\text{-}OR^5$ wherein R^5 is H, C_1-C_4 alkyl or C_2-C_5 alkanoyl; and R^4 is HO, C_1-C_4 alkoxy, C_2-C_5 alkanoyloxy or halo; or R^4 is linked by a double bond and is $=O$ or $=N\text{-}OR^5$; or R^4 is a group of formula (II) wherein R^6 is HO, C_1-C_4 alkoxy, C_2-C_5 alkanoyloxy or halo, or R^6 is linked by a double bond and is $=O$ or $=N\text{-}OR^5$; with certain provisos when R^2 is isopropyl or sec-butyl; are broad spectrum antiparasitic agents useful for treating parasite infestations of livestock and domesticated animals.

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ANTIPARASITIC AGENTS

This invention relates to antiparasitic agents and in particular to compounds for use with domestic companion animals. The compounds are related to the avermectins but have modified substituent groups at the C-23 and C-25 positions. Processes for preparation of the compounds and compositions thereof are also included.

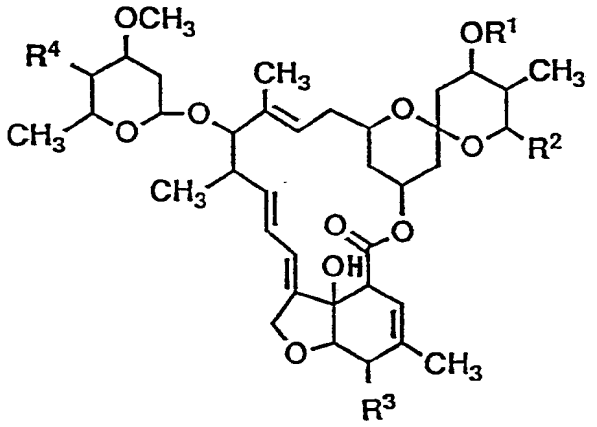
The avermectins and milbemycins form an important group of broad spectrum antiparasitic agents possessing anthelmintic, ectoparasiticidal, insecticidal and antibacterial activity, with application in the areas of animal and human health, agriculture and horticulture. The avermectins are a group of macrolide compounds (previously referred to as C-076 compounds) isolated from the fermentation broth of an avermectin producing strain of Streptomyces avermitilis. In addition to these fermentation derived products, a large number of publications describe compounds derived semisynthetically from these products, many of which possess useful antiparasitic activities. Some of this chemistry is reviewed in Macrolide Antibiotics, Omura S., Ed., Academic press, New York (1984) and by Davies, H.G., Green, R.H. in Natural Product Reports, (1986), 3, 87-121 and in Chem. Soc. Rev., (1991), 20, 211-269 and 271-239. Thus for example U.S. patent no 4200581 discloses avermectin derivatives substituted by hydrocarbon groups.

In our European Patent Application nos. 0214731 and 0317148, we describe the preparation of compounds related to the avermectins but having an unnatural substituent group at the C-25 position in place of the isopropyl or sec-butyl group which is present in the

naturally occurring avermectins.

The present invention provides a series of semi-synthetically derived novel compounds wherein both the C-23 and C-25 position substituents are modified. These compounds form the starting point for a further series of semi-synthetically derived analogues wherein the C-5 and C-13 position substituents may also be modified. The compounds possess a broad spectrum of activity against insect pests, acari, free-living nematodes and parasites affecting animals. Moreover the compounds of the invention possess a number of beneficial properties compared to similar compounds in terms of their efficacy, pharmacokinetics and toleration. The benefits that arise from this unexpected combination of properties include efficacy against the important parasitic worms or arthropods afflicting livestock, domesticated animals or humans at lower doses than are currently employed for related compounds and, in addition, the ability to treat animals previously regarded as sensitive to this class of macrolide with a greater margin of safety.

Thus according to the present invention there are provided compounds having the formula:-



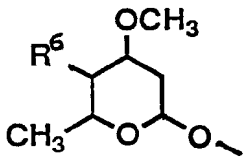
(I)

wherein R^1 is C_1-C_6 alkyl, C_3-C_6 alkenyl, or substituted C_1-C_4 alkyl wherein said substituent is halo, C_1-C_4 alkoxy, C_2-C_5 alkanoyl, C_2-C_5 alkoxycarbonyl, carboxy, mercapto or aryl;

R^2 is C_3-C_8 alkyl, C_3-C_8 alkenyl, C_3-C_8 cycloalkyl or C_5-C_8 cycloalkenyl;

R^3 is OH, C_1-C_4 alkoxy or C_2-C_5 alkanoyloxy; or R^3 is linked by a double bond and is =N-OR^5 wherein R^5 is H, C_1-C_4 alkyl or C_2-C_5 alkanoyl; and

R^4 is HO, C_1-C_4 alkoxy, C_2-C_5 alkanoyloxy or halo; or R^4 is linked by a double bond and is =O or =N-OR^5 wherein R^5 is as previously defined; or R^4 is a group of the formula:



(II)

wherein R^6 is HO, C_1-C_4 alkoxy, C_2-C_5 alkanoyloxy or halo, or R^6 is linked by a double bond and is =O or =N-OR^5 wherein R^5 is as previously defined;

with the proviso that R^2 is not isopropyl or sec-butyl when R^3 is hydroxy, C_1-C_4 alkoxy or C_2-C_5 alkanoyloxy and R^4 is HO, C_1-C_4 alkoxy, C_2-C_5 alkanoyloxy or is a group of the formula (II) wherein R^6 is OH, C_1-C_4 alkoxy or C_2-C_5 alkanoyloxy.

In the above definitions alkyl groups containing 3 or more carbon atoms may be straight or branch-chain; halo means fluoro, chloro, bromo, or iodo; and aryl means phenyl optionally substituted by one or more C_1-C_4 alkyl or C_1-C_4 alkoxy groups or halo atoms.

The C-076 complex comprises eight distinct but closely related compounds described as C-076 A1a, A1b, A2a, A2b, B1a, B1b, B2a and B2b. The "a" series of compounds refers to the natural avermectins wherein the 25-substituent is (S)-sec-butyl and the "b" series to those wherein the 25-substituent is isopropyl. The designations "A" and "B" refer to avermectins wherein the 5-substituent is methoxy or hydroxy, respectively, and the numeral "1" refers to avermectins wherein a double bond is present at the 22-23 position, and

numeral "2" to avermectins lacking the 22-23 double bond and having a hydrogen at the 22-position and hydroxy at the 23 position.

In this specification, the "a" and "b" identifiers have been dropped, however, identifiers A1, A2, B1 and B2 have been retained to refer to non-natural avermectins having the structural features corresponding to those of the natural avermectins as noted above.

Compounds of the formula (I) wherein R^3 is HO (avermectin B derivatives) are generally preferred. R^1 is preferably C_1-C_4 alkyl especially methyl or ethyl; R^2 is preferably cyclohexyl. Also preferred are compounds where R^3 is =N-OH(oximino) or =N-OR^5 wherein R^5 is methyl or ethyl.

The compounds of formula (I) wherein R^4 is α-L-oleandrosyl and R^3 is OH or OCH_3 are prepared from the corresponding C-25 modified avermectin A2 or B2 derivative of formula (I) wherein R^1 is H, by reacting with a halide of the formula R^1-hal wherein hal is bromine or preferably iodine, in the presence of a silver salt.

The reaction is performed by stirring the appropriate avermectin having a hydroxy group at the C-23 position, with the halide in an organic solvent, in the presence of a suitable silver salt, preferably silver salicylate. We have found that diethyl ether is a preferred solvent. A period of several days at room temperature may be required for the reaction to go substantially to completion. Under these conditions we have surprisingly found that the reaction is substantially selective for the C-23 hydroxy group and it is not necessary to protect the C-5 hydroxy group present in the avermectin B class of compounds. The iodide is generally the preferred halide, however in activated compounds e.g. where R^1 is allyl, or benzyl,

the bromide is preferable. The product is isolated after filtration and evaporation of the solvent and is purified if necessary, by chromatography.

Compounds of the formula (I) wherein R^3 is C_1-C_4 alkoxy or C_2-C_5 alkanoyloxy can be prepared from the corresponding C-23 substituted derivative wherein R^3 is hydroxy by conventional alkylation or acylation. Compounds of formula (I) wherein R^3 is $=NOR^5$ are prepared similarly from the corresponding compound wherein R^3 is hydroxy by oxidation, for example using manganese dioxide, to give the 5-oxo intermediate, which is then reacted with hydroxylamine to yield the oxime derivative (R^3=NOH) or with an alkoxylamine or acyloxyamine to give compounds where R^3 is $=NOR^5$ and R^5 is C_1-C_4 alkyl or C_2-C_5 alkanoyl respectively.

Compounds of the formula (I) wherein R^4 is OH (monosaccharide derivatives) are prepared by selective hydrolysis of the appropriate avermectin starting material where R^4 is α-L-oleandrosyl. The terminal sugar hydroxy group, 4' in the case of the monosaccharides or 4'' for the disaccharides, may also be modified. In order to do this selectively, the 5-hydroxy group may need protection and this can be done as for example, its 5-O-t-butyldimethylsilyl derivative. The sugar hydroxy group may then be alkylated or acylated to give compounds where R^4 or R^6 are C_1-C_4 alkoxy or C_2-C_5 alkanoyloxy. Alternatively the groups may be oxidised, for example using N-methyl morpholine oxide and tetrapropylammonium perruthenate, to give the 4' or 4''-oxo compound which may then be converted to the oxime or substituted oxime derivatives as previously described. Appropriate reagents and conditions for the these steps may be determined by reference to literature precedents and to the experimental examples included hereafter.

The starting materials of formula (I) wherein R^1

is H are obtained directly from fermentation as previously described in EP-B-0214731 or EP-A-0317148.

As previously mentioned the compounds of the invention are highly active antiparasitic agents. Thus the compounds are effective in treating a variety of conditions caused by endoparasites including, in particular, helminthiasis which is most frequently caused by a group of parasitic worms described as nematodes and which can cause severe economic losses in swine, sheep, horses and cattle as well as affecting domestic animals and poultry. The compounds are also effective against other nematodes which affect various species of animals including, for example, Dirofilaria in dogs and various parasites which can infect animals and humans including gastro-intestinal parasites such as Ancylostoma, Necator, Ascaris, Strongyloides, Trichinella, Toxocara, Capillaria, Trichuris, Enterobius and parasites which are found in the blood or other tissues and organs such as filiarial worms and the extra intestinal stages of Strongyloides, Trichinella and Toxocara.

The compounds are also of value in treating ectoparasite infections including in particular arthropod ectoparasites such as ticks, mites, lice, fleas, blowfly and biting insects.

The compounds of formula (I) are administered as a formulation appropriate to the specific use envisaged and to the particular species of host animal being treated and the parasite or insect involved. They may be administered by injection, either subcutaneously or intramuscularly. Alternatively they may be administered orally in the form of a capsule, bolus, tablet, chewable tablet or liquid drench, or they may be administered as a pour-on or spot-on formulation or as an implant. Such formulations are prepared in a conventional manner in accordance with standard veterinary practice. Thus injectable formulations may

be prepared in the form of a sterile solution or emulsion. Capsules, boluses or tablets may be prepared by mixing the active ingredient with a suitable finely divided diluent or carrier, additionally containing a disintigrating agent and/or binder such as starch, lactose, talc, or magnesium stereate. A drench formulation may be prepared by dispersing the active ingredient in an aqueous solution together with dispersing or wetting agents. Pour-on or spot-on formulations may be prepared by dissolving the active ingredient in an acceptable liquid carrier vehicle, such as butyl digol, liquid paraffin or non-volatile ester with or without addition of a volatile component such as isopropanol. These formulations will vary with regard to the weight of active compound depending on the species of host animal to be treated, the severity and type of infection and the body weight of the host. Generally for oral or parenteral administration, a dose of from about 0.001 to 10 mg per kg, preferably 0.01 t0 1 mg/kg of animal body weight given as a single dose or in divided doses for a period of from 1 to 5 days will be satisfactory but of course there can be instances where higher or lower dosage ranges are indicated and such are within the scope of this invention.

As an alternative the compounds may be administered with the animal feedstuff and for this purpose a concentrated feed additive or premix may be prepared for mixing with the normal animal feed.

For use as an insecticide the compounds are applied as sprays, dusts, emulsions, pour-on, spot-on formulations and the like in accordance with standard veterinary practice.

The invention is illustrated by the following Examples: Fast atom bombardment (FAB) mass spectrometry was performed on a VG model 7070E mass spectrometer using a sample matrix of glycerol, thiglycerol, water and sodium chloride. Electron impact (EI) mass

spectrometry was performed using a VG model 7070F mass spectrometer. m/z values are quoted for the principal fragments. ^{1}H Nuclear magnetic resonance (NMR) spectral data were obtained on a Nicolet QE 300 spectrometer with a sample concentration of 5 mg/ml in deuterochloroform. The chemical shifts are given in parts per million relative to tetramethylsilane.

EXAMPLE 1

23-Methoxy-22,23-dihydro-25-cyclohexylavermectin B1

A solution of 25-cyclohexylavermectin B2 (50 mg) and methyl iodide (570 mg) in diethyl ether (10 ml) containing a suspension of silver salicylate (200 mg) was stirred at room temperature for 30 hours. The reaction mixture was filtered and the filtrate evaporated to yield a yellow oil. The oil was purified by reverse phase high performance liquid chromatography on a Dupont Zorbax (trade mark) ODS C18 column eluting with a 15:85 mixture of water:methanol. Evaporation of the appropriate fractions gave the product (45 mg) as a white powder.

FAB mass spectrometry:	$(M+Na^+)$ observed at m/z 930 (theoretical 930)
EI mass spectrometry:	623, 440, 363, 331, 247, 219, 195, 179, 167, 145, 135, 113, 95, 87.

^1H NMR as expected for a 22,23-dihydro avermectin B1 with a characteristic peak for the C-23 substituent at δ3.33 (3H,s,$-OCH_3$).

EXAMPLES 2-9

The following Examples were prepared following the method of Example 1 from 25-cyclohexylavermectin B2 using the appropriate iodide (Examples 2-5, 8 and 9) or bromide (Examples 6 and 7).

Ex No.	R^2	R^1	Class	^1H NMR for characteristic fragment of C-23 side-chain.	FAB MS Ion observed/theory	EI MS Fragmentation pattern
2	cyclohexyl	-Et	B	1.165 (t, 3H, $-CH_2\underline{CH_3}$)	967/967	638, 619, 556, 440, 422, 404, 377, 331, 265, 247, 219, 195, 177, 145, 135, 113, 95, 87.
3	"	-nPr	B	0.935 (t, 3H, $-CH_2CH_2\underline{CH_3}$)	981/981	652, 633, 391, 331, 307, 247, 219, 195, 179, 145, 135, 127, 113, 107, 95, 87
4	"	-iPr	B	1.15 (d, 3H, $-CH(\underline{CH_3})_2$), 1.06 (d, 3H, $-CH(\underline{CH_3})_2$)	981/981	651, 391, 331, 307, 247, 219, 195, 145, 135, 129, 113, 87.
5	"	-nBu	B	0.92 (t, 3H, $-CH_2CH_2CH_2\underline{CH_3}$)	995/995	666, 405, 331, 247, 219, 195, 179, 153, 145, 135, 127, 113, 95, 87.
6	"	$-CH_2CH=CH_2$	B	5.61 (dq, 1H, $-CH_2CH=\underline{CH_2}$) 5.27 (dq, 1H, $-CH_2CH=\underline{CH_2}$)	979/979	649, 389, 331, 305, 277, 247, 243, 219, 193, 177, 153, 145, 135, 113, 95, 87.
7	"	$-CH_2C_6H_5$	B	7.2-7.45(m, 5H, $-CH_2C_6\underline{H_5}$)	1029/1029	439,355, 341, 331, 327, 312, 294, 251, 247, 242, 235, 202, 164, 153, 145, 135, 113, 105, 91, 87.
8	"	$-CH_2CH_2OCH_3$	B	3.4 (s, 3H, $-CH_2CH_2O\underline{CH_3}$)	997/997	668,482, 407, 331, 323, 295, 289, 261, 257, 247, 237, 219, 195, 145, 127, 113, 111, 95, 87
9	"	$-(CH_2)_4CO_2CH_3$	B	3.45 (s, 3H, $-(CH_2)_4CO_2\underline{CH_3}$)	1053/1053	463,379, 349, 331, 323, 309, 247, 197, 145, 135, 127, 113, 107, 95, 87.

EXAMPLE 10

23-Methoxy-5-oximino-22,23-dihydro-25-cyclohexyl-avermectin B1

A mixture of 23-methoxy-22,23-dihydro-25-cyclohexylavermectin B1 (1 g) and manganese dioxide (2 g) in dry diethyl ether (30 ml) was stirred at room temperature for 16 hours. Further manganese dioxide (1 g) was then added and stirring continued for a further 5 hours. The mixture was then filtered and the residue washed with dichloromethane (50 ml). The filtrate was evaporated to give 23-methoxy-5-oxo-22,23-dihydro-25-cyclohexylavermectin B1 (1 g) as a yellow foam. This was dissolved in pyridine (10 ml) and hydroxylamine hydrochloride (1 g) was added. The mixture was stirred at room temperature for 3 hours and then concentrated under vacuum to a small volume (3 ml) and partitioned between dichloromethane and 20% aqueous citric acid. The organic layer was separated, washed with 20% citric acid, then water, dried over anhydrous sodium sulphate, filtered and the solvent evaporated to give crude product (1.018 g). The product was purified by column chromatography on silica gel (100 g) eluting with dichloromethane/ethyl acetate (2:1) to give 23-methoxy-5-oximino-22,23-dihydro-25-cyclohexylavermectin B1 (711 mg). The product was further purified by reverse phase high performance liquid chromatography on a Dynamax (trade mark) 5 cm diameter ODS C18 column eluting with a mixture of methanol:water (85:15). Evaporation of appropriate fractions gave the pure title product (298 mg).

FAB mass spectrometry:	($M+Na^+$) observed at m/z 966 (theoretical 966)
EI mass spectrometry:	637, 482, 363, 331, 289, 279, 274, 257, 251, 247, 219, 195, 179, 145, 127, 113, 111, 95, 87.

Selected ^{1}H NMR data (δ):1.93(3H,s); 3.3(3H,s); 3.39 (3H,s); 3.4(3H,s); 8.62(1H,bs).

EXAMPLE 11

23-Methoxy-5-methoximino-22,23-dihydro-25-cyclohexyl-avermectin B1

A solution of 23-methoxy-5-oxo-22,23-dihydro-25-cyclohexylavermectin B1 (0.5 g), prepared as described in Example 10, and methoxylamine hydrochloride (0.5 g) in pyridine (10 ml) was stirred at room temperature for 16 hours. The reaction mixture was poured into water (50 ml) and extracted with diethyl ether (50 ml, x3). The combined ether layers were washed with water (50 ml) and brine (50 ml), dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography on silica gel (50 g) eluting with dichloromethane/ethyl acetate (4:1). Evaporation of appropriate fractions gave 23-methoxy-5-methoximino-22,23-dihydro-25-cyclohexylavermectin B1 which was further purified by reverse phase high performance liquid chromatography on a Dynamax (trade mark) 5 cm diameter ODS C18 column eluting with a mixture of methanol and water. Evaporation of appropriate fractions gave the pure title compound (317 mg).

FAB mass spectrometry: ($M+Na^+$) observed at m/z 980 (theoretical 980)

EI mass spectrometry: 669, 651, 363, 331, 288, 257, 251, 247, 227, 219, 195, 179, 145, 143, 127, 113, 111, 95, 87.

Selected ^{1}H NMR data (δ): 4.0 (3H,s).

EXAMPLE 12

23-Ethoxy-5-oximino-22,23-dihydro-25-cyclohexyl-avermectin B1

To a solution of 23-ethoxy-5-oxo-22,23-dihydro-25-

cyclohexylavermectin B1 (0.8 g, see Preparation 3) in methanol (16 ml) and dioxan (16 ml) was added a solution of hydroxylamine hydrochloride (1 g) in water (16 ml). The mixture was warmed to 50°C and maintained at this temperature for 1 hour. The cooled solution was then evaporated and the residue partitioned between diethyl ether (100 ml) and water (100 ml). The organic layer was separated, washed with aqueous sodium hydrogen carbonate (100 ml, 5% solution) and water (100 ml), dried ($MgSO_4$) and evaporated. The crude product (0.8 g) was purified by column chromatography on silica gel (40 g) eluting with dichloromethane:ethyl acetate (100:0 to 70:30). Combination of appropriate fractions gave 23-ethoxy-5-oximino-22,23-dihydro-25-cyclohexylavermectin B1 (0.5 g). The product was further purified by reverse phase high performance liquid chromatography on a Dynamax (trade mark) 5 cm diameter ODS C18 column eluting with a mixture of methanol:water (90:10). Evaporation of appropriate fractions gave the pure title compound (380 mg).

FAB mass spectrometry:	$(M+Na^+)$ observed at m/z 980 (theorectical 980)
EI mass spectrometry:	377, 331, 293, 289, 274, 265, 257, 247, 219, 195, 179, 145, 127, 113, 111, 95, 87.

Selected ^1H NMR data (δ): 8.31 (bs,1H)

EXAMPLE 13

23-Ethoxy-5-methoximino-22,23-dihydro-25-cyclohexyl-avermectin B1

To a solution of 23-ethoxy-5-oxo-22,23-dihydro-25-cyclohexylavermectin B1 (0.8 g) in methanol (16 ml) and dioxan (16 ml) was added a solution of methoxylamine hydrochloride (0.8 g) in water (16 ml). The mixture was warmed to 50°C and maintained at this temperature for 2 hours. The cooled solution was then evaporated

and the residue partitioned between ether (100 ml) and water (100 ml). The organic layer was separated, washed with aqueous sodium hydrogen carbonate (100 ml), 5% solution) and water (100 ml), dried ($MgSO_4$) and evaporated. The crude product (0.7 g) was purified by column chromatography on silica gel (50 g) eluting with dichloromethane:ethyl acetate (100:0 to 80:20). Evaporation of appropriate fractions gave 23-ethoxy-5-methoximino-22,23-dihydro-25-cyclohexylavermectin B1 (350 mg) as a white amorphous powder.

FAB mass spectrometry: ($M+Na^+$) observed at m/z 994 (theoretical 994)

EI mass spectrometry: 682, 655, 482, 377, 331, 293, 289, 288, 265, 257, 247, 219, 195, 179, 145, 127, 113, 111, 95, 87.

Selected ^1H NMR data (δ): 3.995 (s,3H)

EXAMPLE 14

23-Methoxy-22,23-dihydro-25-cyclohexylavermectin B1 monosaccharide

23-Methoxy-22,23-dihydro-25-cycolohexylavermectin B1 (10 g) was added to a 1% solution of sulphuric acid in isopropanol (100 ml). The mixture was stirred at room temperature for 16 hours. The reaction mixture was poured onto ice (100 g) and water (100 ml) and extracted with dichloromethane (2 x 100 ml). The combined organic extracts were washed with aqueous potassium hydrogen carbonate (50 ml, 20% solution) and water (25 ml), dried ($NaSO_4$) and evaporated to give an off-white solid. This was purified by column chromatography on silica gel (100 g) eluting with dichloromethane:ethyl acetate (2:1 to 1:1). Evaporation of appropriate fractions gave 8.8 g of a white solid 2 g of this solid was further purified by reverse phase high performance liquid chromatography on a Dynamax (trade mark) 5 cm diameter ODS C-18 column

eluting with methanol:water (85:15). Evaporation of appropriate fractions gave 23-methoxy-22,23-dihydro-25-cyclohexyl-avermectin B1 monosaccharide (1.6 g) as a white amorphous powder.

FAB mass spectrometry: ($M+Na^+$) observed at 809 (theoretical 809)

EI mass spectrometry: 624, 482, 363, 331, 279, 261, 251, 247, 227, 195, 179, 145, 143, 127, 113, 111, 95, 87.

Selected ^1H NMR data (δ): 3.46(s,3H), 3.3(s,3H).

EXAMPLE 15

23-Methoxy-5-oximino-22,23-dihydro-25-cyclohexyl-avermectin B1 monosaccharide

A mixture of 23-methoxy-22,23-dihydro-25-cyclohexyl-avermectin B1 monosaccharide (1.2 g) and manganese dioxide (5 g) in anhydrous diethyl ether (30 ml) was stirred for 2 hours. Further manganese dioxide (1 g) was added and stirring continued for 1 hour. The reaction mixture was filtered and evaporated. The residue (1 g) was taken up in methanol (20 ml) and dioxan (20 ml) and a solution of hydroxylamine hydrochloride (1 g) in water (20 ml) was added. The mixture was heated to 50°C for 1 hour, then cooled and evaporated. The residue was partitioned between diethyl ether (100 ml) and water (100 ml). The organic layer was separated, washed with aqueous sodium hydrogen carbonate (100 ml, 10% solution) and water (100 ml), dried (Na_2SO_4) and evaporated to give an oil (1 g) which was purified by column chromatography on silica gel (50 g) eluting with dichloromethane:ethyl acetate (100:0 to 75:25). Evaporation of appropriate fractions gave a foam which was further purified by reverse phase high performance liquid chromatography on a Dynamax (trade mark) 5 cm diameter ODS C-18 column eluting with methanol:water (85:15). Evaporation of appropriate fraction gave 23-methoxy-5-oximino-22,23-

dihydro-25-cyclohexylavermectin B1 monosaccharide (160 mg) as a white amorphous powder.

FAB mass spectrometry: ($M+Na^+$) observed at m/z 822 (theoretical 822)

EI mass spectrometry: 799, 655, 637, 482, 363, 331, 288, 279, 256, 251, 237, 219, 195, 179, 145, 127, 113, 111, 95, 87.

Selected ^1H NMR data (δ): 8.55 (bs,1H)

EXAMPLE 16

23-Methoxy-5-methoximino-22,23-dihydro-25-cyclohexyl-avermectin B1 monosaccharide

A mixture of 23-methoxy-22,23-dihydro-25-cyclohexylavermectin B1 monosaccharide (1.0 g) and manganese dioxide (5 g) in anhydrous diethyl ether (30 ml) was stirred at room temperature for 3 hours, then filtered and evaporated to give a yellow oil (1 g). This was taken up in methanol (15 ml) and dioxan (15 ml) and a solution of methoxylamine (1.0 g) in water (15 ml) added. The mixture was heated at 50°C for 2 hours, cooled and evaporated. The residue was partitioned between diethyl ether (100 ml) and water (100 ml). The organic layer was separated, washed with aqueous sodium hydrogen carbonate (100 ml, 10% solution) and water (100 ml), dried (Na_2SO_4) and evaporated to give an oil (1 g) which was purified by column chromatography on silica gel (40 g) eluting with dichloromethane:ethyl acetate (100:0 to 75:25). Evaporation of appropriate fractions gave a foam which was further purified by reverse phase high performance liquid chromatography on a Dynamax (trade mark) 5 cm diameter ODS C-18 column eluting with methanol:water (90:10). Evaporation of appropriate fraction gave 23-methoxy-5-methoximino-22,23-dihydro-25-cyclohexylavermectin B1 monosaccharide (188 mg) as a white amorphous powder.

FAB mass spectrometry:	($M+Na^+$) observed at m/z 836 (theoretical 836)
EI mass spectrometry:	781, 696, 651, 620, 588, 525, 467, 363, 331, 288, 251, 219, 195, 145, 113, 95, 87.

Selected ^1H NMR data (δ): 3.995 (s,3H).

EXAMPLE 17

23-Ethoxy-5-oximino-22,23-dihydro-25-cyclohexyl-avermectin B1 monosaccharide

To a solution of 23-ethoxy-22,23-dihydro-25-cyclohexyl-avermectin B1 (3.5 g) in isopropanol (35 ml) was added isopropanol (35 ml) containing sulphuric acid (0.7 ml). The mixture was allowed to stand for 16 hours at room temperature, then poured onto ice (175 g) and water 175 ml) and extracted with dichloromethane (200 ml, x2). The combined organic extracts were dried ($MgSO_4$) and evaporated to give a yellow foam (4.2 g); 2 g of which was dissolved in anhydrous diethyl ether (55 ml). To this stirred solution at room temperature was added manganese dioxide (10 g) and stirring continued for 2 hours after which manganese dioxide (1 g) was added and stirring continued for a further ½ hour. The reaction mixture was then filtered and evaporated to give a yellow foam (1.2 g) which was dissolved in methanol (24 ml) and dioxan (24 ml). A solution of hydroxylamine hydrochloride (1.2 g) in water (12 ml) was added. The mixture was stirred for 1 hour at 50°C then cooled and evaporated. The residue was partitioned between diethyl ether (100 ml) and water (100 ml). The organic layer was washed with aqueous sodium hydrogen carbonate (100 ml, 10% solution) and water (100 ml), dried ($MgSO_4$) and evaporated. The product was purified by column chromatography on silica gel (50 g) eluting with dichloromethane:ethyl acetate (100:0 to 80:20). Evaporation of appropriate fractions gave a foam (610 mg). This material was further

purified by reverse phase high performance liquid chromatography on a Dynamax (trade mark) 5 cm diameter ODS C-18 column eluting with methanol:water (85:15). Evaporation of appropriate fractions gave 23-ethoxy-5-oximino-22,23-dihydro-25-cyclohexyl-avermectin B1 monosaccharide (340 mg) as a white amorphous powder.

FAB mass spectrometry: ($M+Na^+$) observed at m/z 836 (theoretical 836)

EI mass spectrometry: 669, 651, 377, 331, 293, 274, 265, 247, 241, 219, 195, 179, 157, 145, 127, 113, 111, 95, 87.

Selected ^1H NMR data (δ): 8.48 (bs,1H)

EXAMPLE 18

4"-Oxo-23-methoxy-22,23-dihydro-25-cyclohexylavermectin B1

To a stirred solution of 5-O-t-butyldimethylsilyl-4"-oxo-23-methoxy-22,23-dihydro-25-cyclohexylavermectin B1 (1.6 g) in methanol (45 ml) maintained at -20°C was added over a period of 5 minutes a solution of para-toluenesulphonic acid (1.2 g) in methanol (120 ml). The reaction mixture was stirred at -20°C for 1 hour and then allowed to warm to 0°C and then stirred for a further 1.5 hours at 0°C. The reaction mixture was partitioned between ethylacetate (700 ml) and aqueous sodium hydrogen carbonate (100 ml, 5% solution). The organic layer was washed with water (200 ml, x3). The organic layer was re-extracted with ethyl acetate (200 ml). The combined ethyl acetate layers were dried and evaporated to give 4"-oxo-23-methoxy-22,23-dihydro-25-cyclohexylavermectin B1 (1.5 g) as a white amorphous foam.

FAB mass specrotmetry: $M+Na^+$) observed at m/z 951 (theoretical 951)

EI mass spectrometry: 624, 363, 331, 279, 261, 255, 251, 247, 227, 195, 179, 145, 143, 127, 113, 111, 95, 87.

Selected ^{1}H-NMR data (δ): 3.47(s,3H), 3.38(s,3H), 3.27(s,3H)

EXAMPLE 19

4"-Oximino-23-methoxy-22,23-dihydro-25-cyclohexyl-avermectin B1

To a stirred solution of 4"-oxo-23-methoxy-22,23-dihydro-25-cyclohexylavermectin B1 (0.7 g) in methanol (14 ml) and dioxan (14 ml) was added a solution of hydroxylamine hydrochloride (0.7 g) in water (14 ml). The mixture was heated at 50°C for 1 hour, then cooled and poured into diethyl ether (200 ml) and water (100 ml). The ether layer was separated and washed with aqueous sodium hydrogen carbonate (100 ml, 5% solution), water (100 ml), brine (100 ml), then dried ($MgSO_4$) and evaporated to give a foam (0.8 g). The products were purified by reverse phase high performance liquid chromatography on a Dynamax (trade mark) 5 cm diameter ODS C18 column eluting with a mixture of methanol:water (85:15). Evaporation of appropriate fractions gave 4"-oximino-23-methoxy-22,23-dihydro-25-cyclohexylavermectin B1 (oxime isomer A eluted first, 80 mg) and (oxime isomer B eluted second, 190 mg).

Isomer A

FAB mass spectrometry: ($M+Na^+$) observed at m/z 966 (theoretical 966)

EI mass spectrometry: 482, 363, 331, 301, 279, 269, 261, 251, 247, 219, 181, 179, 158, 127, 113, 111, 95, 87.

Selected ^{1}H data (δ): 3.42(s,6H), 3.3(s,3H)

Isomer B

FAB mass spectrometry: ($M+Na^+$) observed at m/z 966 (theoretical 966)

EI mass spectrometry: 625, 482, 363, 331, 301, 279, 269, 251, 247, 219, 181, 179, 158, 127, 113, 111, 95, 87.

Selected ^{1}H-NMR data (δ): 3.42(s,3H), 3.30(s,3H), 3.26(s,3H).

EXAMPLE 20

23-Methoxy-22,23-dihydro-25-cyclohexylavermectin A1

A solution of 23-methoxy-22,23-dihydro-25-cyclohexylavermectin B1 (250 mg) and methyl iodide (1 ml) in diethyl ethyl (10 ml) containing a suspension of silver oxide (250 mg) was stirred at room temperature for 48 hours. The reaction mixture was filtered and the filtrate evaporated to yield an oil which was purified by reverse phase high performance liquid chromatography on a Dynamax (trade mark) 5 cm diameter ODS C18 column eluting with a mixture of methanol and water (87:13). Evaporation of appropriate fractions gave pure title compound (139 mgs) as a white amorphous powder.

FAB mass spectrometry: (M+ Na^+) observed at $^m/_z$ 967 (theoretical 967)

EI mass spectrometry: 638, 482, 363, 331, 279, 275, 257, 251, 247, 219, 195, 193, 145, 127, 113, 111, 95, 87.

Selected ^{1}H-NMR data (δ): 3.51(s,3H), 3.41(s,3H), 3.39(s,3H), 3.30(s,3H).

EXAMPLE 21

23-Methoxy-4'-oximino-22,23-dihydro-25-cyclohexyl-avermectin B1 monosaccharide

A solution of 5-O-t-butyldimethylsilyl-23-methoxy-4'-oxo-22,23-dihydro-25-cyclohexylavermectin B1 monosaccharide (86 mg) and hydroxylamine hydrochloride (86 mg) in pyridine (2 ml) was stirred at room temperature for one hour. The mixture was poured into

water (10 ml) and extracted with diethyl ether (20 ml). The organic layer was separated, washed with 10% aqueous citric acid solution (10 ml), water (10 ml) and brine (10 ml), then dried (Na_2SO_4), filtered and evaporated to yield an opaque glass (75 mg). The product was purified by column chromatography on silica gel (Merck 9385 (trade mark)) eluted with 10% ethyl acetate in dichloromethane. Combination and evaporation of appropriate fractions gave an opaque glass (30 mg) which was further purified by reverse phase high performance liquid chromatography on an Ultrasphere (trade mark) 10 mm diameter ODS C-18 column eluted with acetonitrile:methanol:water (83:12:5). Combination and evaporation of appropriate fractions gave a colourless gum which was taken up in methanol (10 ml) containing para-toluene sulphonic acid (0.5 mg). The reaction mixture was maintained at room temperature for 1½ hours and then poured into aqueous potassium hydrogen carbonate solution (10 ml) and diethyl ether (20 ml). The organic layer was separated, washed with water (10 ml), brine (10 ml) then dried (Na_2SO_4), filtered and evaporated to give crude product (19.2 mg). This was purified by reverse phase high performance liquid chromatography on an Ultrasphere (trade mark) 10 mm diameter ODS C-18 column eluted with acetonitrile:methanol:water (61:14:25). Evaporation of appropriate fractions gave the title compound (13.8 mg) as a white amorphous powder.

FAB mass spectrometry:	$(M+Na^+)$ observed at $^m/z$ 822 (theoretical 822)
EI mass spectrometry:	625, 363, 279, 261, 251, 195, 179, 158, 135, 111, 95
Selected ^1H NMR data (δ):	7.25 (bs,1H)

EXAMPLE 22

4'-epi-Hydroxy-23-methoxy-22,23-dihydro-25-cyclohexyl-avermectin B1 monosaccharide

To a solution of 5-O-t-butyldimethylsilyl-4'-oxo-23-methoxy-22,23-dihydro-25-cyclohexylavermectin B1 monosaccharide (1.17 g) in methanol (50 ml) was added sodium borohydride (100 mg). After ½ hour the reaction mixture was poured into water (100 ml) and extracted with ether (50 ml, x 3). The combined organic layers were washed with water (20 ml, x 2), brine (20 ml), dried (Na_2SO_4), filtered and evaporated to give crude product which was purified by reverse phase high performance liquid chromatography on a Dynamax (trade mark) 5 cm diameter column eluted with methanol:water (90:10). Evaporation of appropriate fractions gave a gum (609 mg). 150 mg of this material was taken up in methanol (10 ml) containing para-toluene sulphonic acid (0.5 mg). After 1 hour at room temperature the reaction mixture was poured into aqueous saturated sodium hydrogen carbonate solution (20 ml) and extracted with ether (20 ml, x 3). The combined organic layers were washed with water (10 ml, x 3), brine (10 ml, x 2), dried (Na_2SO_4), filtered and evaporated to give a yellow foam (95 mg). This was purified by column chromatography on silica gel (Merck 9385 (trade mark), 2 g) eluted with dichloromethane: ethyl acetate (4:1). Combination and evaporation of appropriate fractions gave the title compound (75.4 mg) as a white amorphous powder.

FAB mass spectrometry:	$(M+Na^+)$ observed at $^m/_z$ 809 (theoretical 809).
EI mass spectrometry:	642, 363, 331, 279, 261, 251, 247, 219, 195, 179, 145, 127, 113, 111, 95, 87.
Selected ^1H NMR data (δ):	3.82 (bs,1H).

EXAMPLE 23

4',5-Bis-oximino-23-methoxy-22,23-dihydro-25-cyclohexylavermectin B1 monosaccharide

A solution of 4'-oximino-23-methoxy-22,23-dihydro-25-cyclohexylavermectin B1 monosaccharide (64 mg) in diethyl ether (20 ml) containing manganese dioxide (64 mg) was stirred at room temperature for 48 hours. The reaction mixture was filtered and the filter cake washed with dichloromethane. The combined filtrates were evaporated to give a yellow gum which was taken up in methanol (10 ml) and dioxan (10 ml). To this solution was added a solution of hydroxylamine hydrochloride (100 mg) in water (5 ml). The reaction mixture was stirred at room temperature for 36 hours then poured into aqueous potassium hydrogen carbonate solution (20 ml) and extracted with ether (20 ml, x 2). The combined organic layers were dried (Na_2SO_4), filtered and evaporated. The crude product was purified by reverse phase high performance liquid chromatography on an Ultrasphere (trade mark) 10 mm diameter ODS C-18 column eluted with methanol:water (80:20). Evaporation of appropriate fractions gave the title compound (5.6 mg) as a white amorphous powder.

FAB mass spectrometry:	$(M+Na^+)$ observed at $^m/_z$ 835 (theoretical 835)
EI mass spectrometry:	748, 722, 596, 578, 469, 424, 378, 354, 333, 264, 249, 221, 197, 179, 161, 145, 113, 91.
Selected ^1H NMR data (δ):	8.4 (bs,1H), 7.55(bs,1H).

PREPARATION 1

5-O-t-Butyldimethylsilyl-23-methoxy-22,23-dihydro-25-cyclohexyl-avermectin B1 and 4",5-bis-O-t-butyl-dimethylsilyl-23-methoxy-22,23-dihydro-25-cyclohexyl-avermectin B1

To a solution of 23-methoxy-22,23-dihydro-25-cyclohexylavermectin B1 (29.6 g) and imidazole (12.7 g) in anhydrous dimethylformamide (280 ml) was added t-butyldimethylsilyl chloride (14.2 g) and the mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under vacuum to approximately 100 ml and then partitioned between diethyl ether (500 ml) and water (150 ml). The aqueous layer was separated and washed with diethyl ether (100 ml, x2). The combined ether layers were washed with water (200 ml, x4) and brine (200 ml), then dried ($MgSO_4$) and evaporated to an oil (35 g). The oil was taken up in the minimum volume of dichloromethane and applied to a column of silica gel (1000 g). Elution with dichloromethane containing 5% ethyl acetate provided, after evaporation of appropriate fractions, 4",5-O-t-butyldimethylsilyl-23-methoxy-22,23-dihydro-25-cyclo-hexylavermectin B1 (13.7 g). Elution with dichloromethane containing 25% ethyl acetate provided, after evaporation of appropriate fractions, 5-O-t-butyldimethylsilyl-23-methoxy-22,23-dihydro-25-cyclohexylavermectin B1 (17.1 g). Both compounds were obtained as amorphous white foams. They were characterised by ^{1}H-NMR and mass spectrometry.

PREPARATION 2

5-O-t-Butyldimethylsilyl-4"-oxo-23-methoxy-22,23-dihydro-25-cyclohexylavermectin B1

To a stirred solution of 5-O-t-butyldimethylsilyl-23-methoxy-22,23-dihydro-25-cyclohexylavermectin B1 (2.9 g) and N-methyl-morpholine oxide (3.71 g) in anhydrous dichloromethane (60 ml) containing a

suspension of crushed 4A° molecular sieves (100 mg) at room temperature was added tetrapropylammonium perruthenate (0.406 g). The mixture was stirred for 1 hour and then filtered. The filtrate was washed with aqueous sodium sulphite (30 ml, 5% solution), brine (30 ml) and aqueous copper sulphate (30 ml, 5% solution). The organic solution was dried ($MgSO_4$) and evaporated. The resulting dark foam was purified by column chromatography on silica gel (100 g) eluting with dichloromethane:ethylacetate (100:0 to 90:10). Combination of appropriate fractions gave 5-O-t-butyldimethylsilyl-4"-oxo-23-methoxy-22,23-dihydro-25-cyclohexylavermectin B1 as a white amorphous foam (1.6 g) which was characterised by ^{1}H-NMR and mass spectrometry.

PREPARATION 3

23-Ethoxy-5-oxo-22,23-dihydro-25-cyclohexylavermectin B1

A mixture of 23-ethoxy-22,23-dihydro-25-cyclohexylavermectin B1 (2 g) and manganese dioxide (4 g) in anhydrous diethyl ether (60 ml) was stirred at room temperature for 16 hours, further manganese dioxide (1 g) was then added and stirring continued for 48 hours. The mixture was then filtered and evaporated to give 23-ethoxy-5-oxo-22,23-dihydro-25-cyclohexylavermectin B1 as a yellow solid (1.6 g) which was used without purification.

PREPARATION 4

5-O-t-Butyldimethylsilyl-23-methoxy-22,23-dihydro-25-cyclohexylavermectin B1 monosaccharide

To a solution of 23-methoxy-22,23-dihydro-25-cyclohexyl avermectin B1 monosaccharide (3 g) and imidazole (3.1 g) in anhydrous dimethylformamide (20 ml) was added t-butyldimethylsilylchloride (0.53 g) and the mixture was stirred overnight then a further 0.27 g

of t-butyldimethylsilyl chloride was added and stirring continued for 2 hours. The reaction mixture was poured into water (100 ml) and extracted with dichloromethane (50 ml, x 2). The combined organic layers were washed with water (50 ml), dried (Na_2SO_4), filtered and evaporated. The product was purified by column chromatgraphy on silica gel (Merck 9385 (trade mark), 50 g) eluted with dichloromethane and then 20% ethyl acetate in dichloromethane. Evaporation of appropriate fractions gave the title compound (3.27 g) as an amorphous white foam which was characterised by ^{1}H-NMR and mass spectrometry.

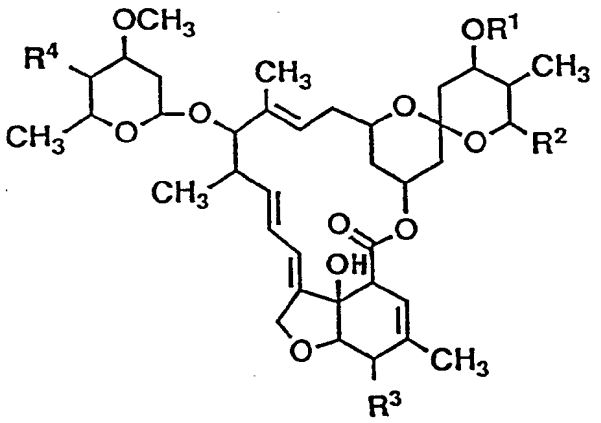
PREPARATION 5

5-O-t-Butyldimethylsilyl-4'-oxo-23-methoxy-22,23-dihydro-25-cyclohexylavermectin B1 monosaccharide

A solution of 5-O-t-butyldimethylsilyl-23-methoxy-22,23-dihydro-25-cyclohexylavermectin B1 monosaccharide (1.4 g), N-methylmorpholine N-oxide (3.14 g), tetrapropylammonium peruthenate (0.233 g) in dichloromethane (300 ml) containing a suspension of powdered 4 angstrom molecular sieves was stirred for 1 hour at room temperature. The reaction mixture was then washed with aqueous sodium sulphite solution (5%, 50 ml, x 2), water (50 ml) and brine (50 ml), then dried (Na_2SO_4), filtered and evaporated. The product was purified by column chromatography on silica gel (Merck 9385 (trade mark), 20 g) eluted with dichloromethane and then 10% ethyl acetate in dichloromethane. Evaporation of appropriate fractions gave the title compound (1.17 g) which was characterised by ^{1}H-NMR and mass spectrometry.

CLAIMS

1. A compound having the formula:



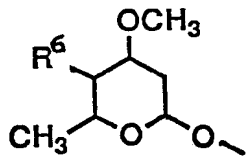
(I)

wherein R^1 is C_1-C_6 alkyl, C_3-C_6 alkenyl, or substituted C_1-C_4 alkyl wherein said substituent is halo, C_1-C_4 alkoxy, C_2-C_5 alkanoyl, C_2-C_5 alkoxycarbonyl, carboxy, mercapto or aryl;

R^2 is C_3-C_8 alkyl, C_3-C_8 alkenyl, C_3-C_8 cycloalkyl or C_5-C_8 cycloalkenyl;

R^3 is OH, C_1-C_4 alkoxy or C_2-C_5 alkanoyloxy; or R^3 is linked by a double bond and is $=N-OR^5$ wherein R^5 is H, C_1-C_4 alkyl or C_2-C_5 alkanoyl; and

R^4 is HO, C_1-C_4 alkoxy, C_2-C_5 alkanoyloxy or halo; or R^4 is linked by a double bond and is =O or $=N-OR^5$ wherein R^5 is as previously defined; or R^4 is a group of the formula:



(II)

wherein R^6 is HO, C_1-C_4 alkoxy, C_2-C_5 alkanoyloxy or

halo, or R^6 is linked by a double bond and is =O or =N-OR^5 wherein R^5 is as previously defined; with the proviso that R^2 is not isopropyl or sec-butyl when R^3 is hydroxy, C_1-C_4 alkoxy or C_2-C_5 alkanoyloxy and R^4 is HO, C_1-C_4 alkoxy, C_2-C_5 alkanoyloxy or is a group of the formula (II) wherein R^6 is OH, C_1-C_4 alkoxy or C_2-C_5 alkanoyloxy.

2. A compound as claimed in claim 1 wherein R^3 is OH.

3. A compound as claimed in claim 1 wherein R^3 is =N-OR^5 and R^5 is H, methyl or ethyl.

4. A compound as claimed in any one of claims 1 to 3 wherein R^1 is C_1-C_4 alkyl.

5. A compound as claimed in claim 4 wherein R^1 is methyl or ethyl.

6. A compound as claimed in any one of claims 1 to 5 wherein R^2 is cyclohexyl.

7. A compound as claimed in any one of claims 1 to 6 wherein R^4 is H or α-L-oleandrosyl.

8. A composition for the treatment and prevention of parasitic infections in humans and animals, including ectoparasiticidal, insecticidal, acaricidal and anthelmintic compositions, which comprises a compound of the formula (I) as claimed in any one of claims 1 to 7 together with an inert diluent or carrier.

9. A composition as claimed in claim 8 in the form of a liquid drench or an oral, pour-on or spot on formulation or in the form of an animal feedstuff or a premix or supplement for addition to animal feed.

10. A method of combating insect or parasite infections or infestations, including parasitic conditions in humans and animals and agricultural or horticultural pest infestations, which comprises applying an effective amount of a compound of the

formula (I) as claimed in any one of claims 1 to 7 to the organism responsible for said infection or infestation or to the location thereof.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 93/00036

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07H17/08; A01N43/90; A61K31/70; A23K1/17

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07H ; C07D ; A01N ; A61K A23K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X,Y	EP,A,0 008 184 (MERCK AND CO. INC.) 20 February 1980 see claims; example 5	1-10
Y	EP,A,0 307 224 (AMERICAN CYANAMID COMPANY) 15 March 1989 see claims	1,2,4,5, 8-10
Y	EP,A,0 238 258 (GLAXO GROUP LIMITED) 23 September 1987 see claims; example 12	1,3-5, 8-10
Y	EP,A,0 214 731 (PFIZER LIMITED) 18 March 1987 cited in the application see claims; example 14	1,6-10

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
29 APRIL 1993	01. 06. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	DAY G.J.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

EP 9300036
SA 69414

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 29/04/93

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		AU-B- 526571	20-01-83
		AU-A- 4923379	07-02-80
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		JP-B- 2038596	31-08-90
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		JP-A- 1156991	20-06-89
		US-A- 5104871	14-04-92
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		AU-A- 6990987	17-09-87
		AU-B- 612565	18-07-91
		AU-A- 6991487	17-09-87
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		SE-A- 8701019	13-09-87
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